Perfusion/ventilation mismatch during exercise in chronic heart failure: an investigation of circulatory determinants

Adrian P Banning, Neil P Lewis, David B Northridge, J Stuart Elborn, Andrew H Henderson

Abstract

***Background*—The ventilatory cost of carbon dioxide (CO_2) elimination on exercise (VE/VCO_2) is increased in chronic heart failure (CHF). This reflects increased physiological dead space ventilation secondary to mismatching between perfusion and ventilation during exercise. The objectives of this study were to investigate the relation of this increased VE/VCO_2 slope to the syndrome of CHF or to limitation of the exercise related increase of pulmonary blood flow, or both.**

***Patients and methods*—Maximal treadmill exercise tests with respiratory gas analysis were performed in 45 patients with CHF (defined as resting left ventricular ejection fraction < 40% on radionuclide scan); 15 normal controls; 23 patients with coronary artery disease and normal resting left ventricular function; and 13 pacemaker dependent patients (six with and seven without CHF) directly comparing exercise responses in rate responsive and fixed rate mode.**

***Results*—Patients with CHF had a steeper VE/VCO_2 slope than normal controls: this was related inversely to peak VO_2 below 20 mol/min/kg. In patients with coronary artery disease in whom peak VO_2 (at respiratory exchange ratio > 1) was as limited as in the patients with CHF but resting left ventricular function was normal, the VE/VCO_2 slope was normal. In pacemaker dependent patients fixed rate pacing resulted in lower exercise capacity and peak VO_2 than rate responsive pacing; the VE/VCO_2 slope was normal in patients without CHF but steeper than normal in patients with CHF; the VE/VCO_2 slope was steeper during fixed rate than during rate responsive pacing in these patients with CHF.**

***Conclusions*—These findings suggest that the perfusion/ventilation mismatch during exercise in CHF is related to the chronic consequences of the syndrome and not directly to limitation of exercise related pulmonary flow. Only when the syndrome of CHF is present can matching between perfusion and ventilation be acutely influenced by changes in pulmonary flow.**

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Keywords: chronic heart failure; perfusion and ventilation during exercise; carbon dioxide elimination

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Ventilation is increased relative to workload in chronic heart failure (CHF).[1 2] This is in part the result of increased production of carbon dioxide (CO_2) from bicarbonate buffering of the lactic acid produced by anaerobic metabolism of exercising skeletal muscle at a lower than normal workload.[3 4] It also reflects a greater ventilatory cost of CO_2 excretion during exercise as reflected in a steeper slope of the linear relation of minute ventilation to CO_2 production (VE/VCO_2)[5-7] with maintenance of normal blood gas concentrations.[2 6 8 9] The increase in the steepness of the VE/VCO_2 slope reflects an increase in physiological dead space ventilation during exercise, attributable to mismatching between perfusion and ventilation.[5 7] The slope is related to the severity of the functional limitation, being inversely related to exercise tolerance and peak VO_2.[5 9] It has been shown not to correlate with haemodynamic variables such as pulmonary capillary wedge pressure.[2 10]

CHF is associated with several factors that might influence pulmonary perfusion/ventilation matching. These include the direct consequences of a smaller increase in exercise cardiac output (and thus in total pulmonary flow during exercise) than in normal individuals and also non-cardiac poorly understood components of the syndrome of CHF (for example, vascular), reflecting the chronic compensatory response to impaired cardiac performance.

This study addresses the question is "exercise related perfusion/ventilation mismatch related directly to limitation of overall pulmonary flow during exercise or is it a chronic feature of the CHF syndrome?" In this study we chose to characterise CHF according to the presence of impaired resting left ventricular function, to represent the stimuli for the chronic compensatory responses of CHF. We measured exercise responses in a group of patients with CHF and compared them with a group of normal controls. These largely confirmatory studies then provided the basis against which we carried out two further discriminatory studies. First, the VE/VCO_2 slope was measured in patients in whom exercise tolerance and peak VO_2 were limited by exercise induced myocardial ischaemia as in the patients with CHF, but in whom resting left ventricular function was normal. The respiratory exchange ratio (VCO_2/VO_2) at peak exercise in these patients was >1, indicative of limitation of skeletal muscle perfusion comparable to that in patients with CHF, implying

that exercise was similarly limited by cardiac output. Second, we investigated whether the VE/V_{CO_2} slope could be altered acutely by reducing the increase in exercise cardiac output and pulmonary flow, by studying pacemaker dependent patients in whom we were able to compare the exercise responses in fixed rate and rate responsive pacing modes.

Patients and methods

PATIENT GROUPS

Group 1 comprised 45 patients (35 men and 10 women of mean (SD) age 51 (11) years) with clinically stable chronic heart failure. Chronic heart failure is defined here as chronic impairment of resting left ventricular function as measured by radionuclide left ventricular ejection fraction <40%. Heart failure was of mixed aetiology: 36 patients (mean (SD) age 59 (9) years, of whom 25 were men) had ischaemic heart disease (IHD) but no angina and no electrocardiographic evidence of inducible myocardial ischaemia during exercise; nine patients (mean (SD) age 41 (11) years of whom eight were men) had dilated cardiomyopathy (DCM). Treatment, continued throughout the study, comprised frusemide (mean 60 mg daily) in all patients, digoxin in 10, and angiotensin converting enzyme inhibitors in 13. Two patients were in New York Heart Association (NYHA) functional class I, 19 in class II, 18 in class III, and six in class IV. No patient had clinical or radiographic evidence of fluid retention, pulmonary oedema, or thromboembolic or bronchopulmonary disease.

In 15 of these 45 patients (mean (SD) age 47 (8) years, of whom 12 were men, 11 with IHD, and four with DCM), arterial blood was sampled through a brachial artery cannula, allowing calculation of the ratio of dead space to tidal volume (V_d/V_t) from $PaCO_2$ and mixed expired CO_2 ($PeCO_2$).

Group 2 comprised 15 normal individuals (mean (SD) age 43 (18) years, of whom eight were men) who were similarly studied.

Group 3 comprised 23 patients with coronary artery disease and exercise induced myocardial ischaemia, all of whom had normal resting left ventricular function (ejection fraction >50%). Treatment, discontinued 24 h before the test, consisted of a nitrovasodilator and a calcium antagonist in all patients, and a β adrenoceptor antagonist in all but three. Data were analysed separately for (i) a subgroup of 12 patients (mean (SD) age 58 (7) years, of whom 10 were men) with a peak V_{O_2} < 20 ml/min/kg (13·7 (3·9) ml/min/kg) and (ii) a subgroup of 11 patients (mean (SD) age 58 (9) years, of whom nine were men) with a peak V_{O_2} > 20 ml/min/kg (24·6 (3·2) ml/min/kg). In the first subgroup nine patients had significant three vessel disease and three significant two vessel disease; in the second subgroup six had three vessel disease, four two vessel disease, and one single vessel disease. The respiratory exchange ratio (V_{CO_2}/V_{O_2}) was >1 at peak exercise in all patients.

Group 4 comprised 13 patients (mean (SD) age 66 (9) years, of whom nine were men) whose pacemakers had been implanted >2 years previously and who were maintained with rate responsive pacing (six with dual chamber pacemakers and seven with rate responsive ventricular pacemakers). Six patients (mean (SD) age 68 (7) years, of whom five were men; three with dual chamber pacemakers and three with rate responsive ventricular pacemakers) had treated chronic heart failure of mixed aetiology (two IHD, three DCM, and one after total correction of Fallot's tetralogy), defined and characterised as in group 1. Treatment, continued throughout the study, comprised frusemide (mean 60 mg daily) in all patients and a calcium antagonist in one. A control group was provided by seven patients (mean (SD) age 65 (3) years, of whom four were men; three with dual chamber pacemakers and four with rate responsive ventricular pacemakers) with no other known cardiovascular disease and normal resting left ventricular function (ejection fraction > 50%).

PROTOCOL

All patients underwent maximal symptom limited treadmill exercise testing > 2 h after food using either the Weber protocol[11] (groups 1, 2, and 4) or standard Bruce protocol (group 3). Blood pressure, heart rate, and 12 lead electrocardiogram were recorded at rest, the end of each 2 min stage of exercise, and peak exercise. Expired gases were sampled during exercise by a mass spectrometer using the argon dilution technique[12] to give on line measurement of minute ventilation (VE), minute C_{O_2} production (V_{CO_2}) and minute oxygen consumption (V_{O_2}), as previously reported.[6] Respiratory rate (Fbr) was recorded over the final 30 s of each exercise stage. Peak V_{O_2} was determined from the mean V_{O_2} over the final 30 s of exercise. The relation during exercise between VE and V_{CO_2} was analysed by linear regression:

$$VE = m\,V_{CO_2} + c$$

where m is the slope of VE/V_{CO_2} and c is the VE axis intercept). Figure 1 illustrates the linear VE/V_{CO_2} response recorded in real time during exercise, this relation being linear in every patient ($r > 0{\cdot}92$ in every case).

In a representative subgroup of patients with chronic heart failure, ethical approval was obtained for arterial blood to be sampled via a brachial artery cannula for measurement of pH, arterial oxygen pressure (Pa_{O_2}), arterial carbon dioxide pressure ($Pa\ C_{O_2}$), and bicarbonate and lactate concentrations. Physiological dead space (V_D) was calculated from $PaCO_2$, mixed expired C_{O_2} ($PeCO_2$) and tidal volume (V_T), after correcting for equipment dead space, according to the Bohr equation:

$$V_D = \frac{PaCO_2 - PeCO_2}{PaCO_2} \cdot V_T$$

The physiological dead space was then expressed in relation to tidal volume (V_D/V_T).[13]

Table 1 Haemodynamic and respiratory data during treadmill exercise in patients with chronic heart failure (CHF) and in normal controls

	Patients with CHF (n = 45)	*Normal controls (n = 15)*
Exercise duration (min)	11·4 (6·6)*	23·7 (6·1)
Peak V_{O_2} (ml/min/kg)	16·7 (7·2)*	29·7 (7·2)
RERmax (V_{CO_2}/V_{O_2})	1·12 (0·15)	1·20 (0·12)
VE/V_{CO_2}		
m	38 (13)*	26 (5)
c (l/min)	3·2 (2·9)	2·6 (2·2)
r	0·98 (0·01)	0·99 (0·01)

Values are mean (SD). *P < 0·05 *v* normal controls (Student's *t* test). Peak V_{O_2}, oxygen consumption at peak exercise, RERmax, respiratory exchange ratio at peak exercise; V_{CO_2}, minute carbon dioxide production; VE/V_{CO_2}, minute ventilation/minute carbon dioxide production; *m*, slope of VE/V_{CO_2}; *c*, intercept; *r*, linear regression correlation coefficient.

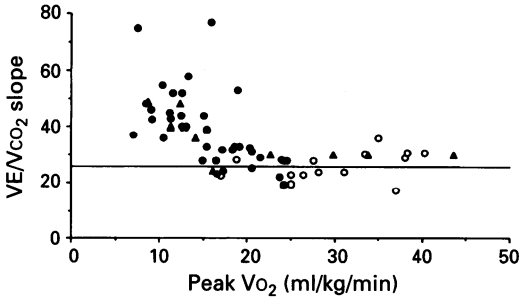

Figure 2 Minute ventilation/minute carbon dioxide production (VE/V_{CO_2}) slope plotted as function of maximal oxygen consumption (peak V_{O_2}) in normal controls (○) and patients with ischaemic heart disease (●) or dilated cardiomyopathy (▲). The solid line represents the group mean (SD) (26 (5)) for controls. Note that the inverse relation between the VE/V_{CO_2} slope and peak V_{O_2} below peak V_{O_2} about 20 ml/min/kg in chronic heart failure is independent of aetiology.

Pacemaker dependent patients, normally maintained in rate responsive mode, performed two exercise tests in random order (single blind) with 30 min recovery between tests: (i) rate responsive ventricular pacing or dual chamber (resting demand rate 70 beats/min) and (ii) fixed rate ventricular pacing (resting demand rate 50 beats/min).

INFORMED CONSENT

The study protocols were approved by the Ethical Committee of the University Hospital of Wales and informed consent was obtained in each case.

STATISTICAL ANALYSIS

Data are reported as group mean (SD). The significance of differences between groups was tested using Student's *t* test for paired or unpaired data as appropriate. P < 0·05 was considered significant.

Results

EXERCISE VENTILATION RESPONSE IN PATIENTS WITH CHRONIC HEART FAILURE AND IN NORMAL INDIVIDUALS

The VE/V_{CO_2} slope was significantly steeper in patients with heart failure (group 1) than in normal individuals (group 2). Table 1 shows no significant difference in the correlation coefficient between the two groups or in the intercept (*c*) of the relation. The respiratory exchange ratio (V_{CO_2}/V_{O_2}) at peak symptom limited exercise (RERmax) was >1 in all participants of both groups, demonstrating that exercise was near to the physiological maximum. Figure 1 shows representative examples of the linear VE/V_{CO_2} relation during exercise in a patient with chronic heart failure and in a normal control. The VE/V_{CO_2} slope was inversely related to peak V_{O_2} in patients whose peak V_{O_2} was <20 ml/min/kg ($r = -0·87$) (fig 2). Figure 2 also shows that the relation seems to be independent of the aetiology of heart failure.

Table 2 gives data of the 15 patients with chronic heart failure in whom arterial blood gases were monitored during exercise. Arterial $PaCO_2$ remained constant, raised lactate levels were not associated with any change in pH on exercise, and PaO_2 increased slightly. The VE/V_{CO_2} slope correlated with V_D/V_T measured at maximal exercise ($r = 0·86$) (fig 3).

PATIENTS WITH CORONARY ARTERY DISEASE AND NORMAL RESTING LEFT VENTRICULAR FUNCTION

Figure 4 shows that the VE/V_{CO_2} slope in patients with coronary artery disease and normal resting left ventricular function (group 3) remained normal and independent of peak V_{O_2}, in contrast to patients with chronic heart failure (group 1) in whom the VE/V_{CO_2} slope was increased at peak V_{O_2} below about 20 ml/min/kg. This was confirmed by separate

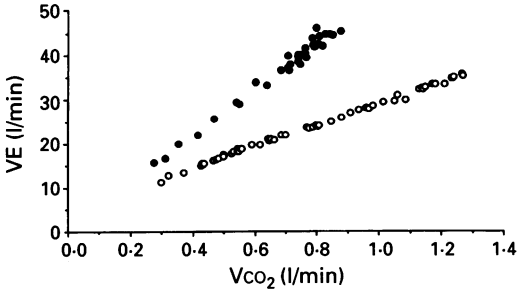

Figure 1 Representative examples showing a steeper minute ventilation/minute carbon dioxide production (VE/V_{CO_2}) linear relation in a patient with chronic heart failure (●) than in a normal control (○).

Table 2 Arterial blood gas and respiratory data from 15 patients with chronic heart failure during treadmill exercise

	Rest	*Maximum exercise*
Peak V_{O_2} (ml/min/kg)	—	15·6 (4·1)
RER max*	—	1·13 (0·09)
VE/V_{CO_2} slope	—	39 (6)
PaO_2 (mm Hg)	97 (11)	108 (14)*
$PaCO_2$ (mm Hg)	38 (6)	36 (6)
pH	7·42 (0·04)	7·42 (0·06)
Lactate (mmol/l)	0·9 (0·3)	3·9 (1·0)*
Bicarbonate (mmol/l)	26·0 (4·5)	21·7 (5·1)*
VE (l/min)	13·1 (4·0)	47·2 (10·2)*
Fbr (per min)	17 (4)	37 (12)*
V_T (l)	0·76 (0·15)	1·27 (0·30)*
V_D/V_T	0·57 (0·11)	0·42 (0·14)*

Values are mean (SD). *P < 0·05 *v* rest (paired *t* test). PaO_2, arterial oxygen pressure; $PaCO_2$, arterial carbon dioxide pressure; Fbr, respiratory rate; V_T, todal volume; VD, physiological dead space; other abbreviations as given in table 1.

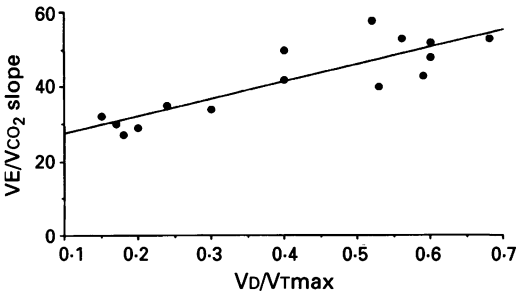

Figure 3 Minute ventilation/minute carbon dioxide production (VE/V_{CO_2}) slope, plotted as a function of V_D/V_T at maximal exercise (V_D/V_T max) in 15 patients with chronic heart failure (linear regression r = 0·86, P < 0·001).

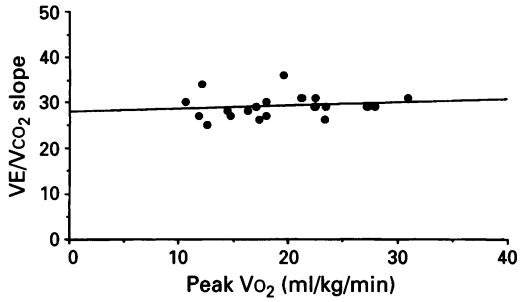

Figure 4 Minute ventilation/minute carbon dioxide production (VE/V_{CO_2}) slope plotted as function of maximal oxygen consumption (peak V_{O_2}) in patients with coronary artery disease and normal resting left ventricular function. Note the lack of an inverse relation between the VE/V_{CO_2} slope and peak V_{O_2} in contrast to that of patients with chronic heart failure (in fig 2).

Table 3 Exercise responses in patients with normal resting LV function but exercise induced myocardial ischaemia and RERmax > 1·0

	Peak V_{O_2} < 20 ml/min/kg (n = 12)	*Peak V_{O_2} > 20 ml/min/kg (n = 11)*
Exercise duration (min)	8·7 (1·6)	10·2 (2·1)
Peak V_{O_2} (ml/min/kg)	13·7 (3·9)*	24·6 (3·2)
RERmax (V_{CO_2}/V_{O_2})	1·01 (0·01)	1·11 (0·06)
VE/V_{CO_2}		
m	29 (4)	29 (2)
c (l/min)	2·8 (1·3)	3·1 (1·11)
r	0·97 (0·03)	0·97 (0·03)

Values are mean (SD). *P < 0·05 *v* patients with peak V_{O_2} > 20 ml/min/kg (Student's *t* test). Abbreviations as given in table 1.

analysis of patients with peak V_{O_2} < 20 ml/min/kg (table 3). Peak V_{O_2} for this patient subgroup was similar to that in patients with CHF (group 1) (13·7 (3·9) *v* 16·7 (7·2) ml/min/kg). The respiratory exchange ratio at peak exercise was also >1 in all patients, indicating near maximal exercise capacity independent of the limiting symptom. The VE/V_{CO_2} slope was not increased, however, as it was in the patients with heart failure (group 1), but was similar to that in normal controls (group 2).

EFFECT OF ACUTE CHANGE IN CHRONOTROPIC RESPONSE TO EXERCISE IN PACEMAKER DEPENDENT PATIENTS

The pacemaker dependent patients with CHF (group 4) had a lower exercise duration and peak V_{O_2}, in both pacing modes, than those with normal resting left ventricular function (table 4). They were also characterised by a steeper VE/V_{CO_2} slope, in each pacing mode, than those without CHF. Figure 5 shows that the data points relating VE/V_{CO_2} slope to peak V_{O_2} in the pacemaker dependent patients with and without CHF (group 4) fell within the same distribution as those of the non-paced patients with CHF (group 1) illustrated in fig 2. The respiratory exchange ratio at peak exercise was >1 in all tests.

Fixed rate pacing, with loss of the chronotropic response to exercise, led to a significantly lower exercise duration and peak V_{O_2} than rate responsive pacing in patients with and without CHF (table 4). In patients with CHF, fixed rate pacing was also associated with a significantly steeper VE/V_{CO_2} slope than rate responsive pacing. In patients with normal resting left ventricular ejection fraction, the VE/V_{CO_2} slope was similar in the two pacing modes. Thus, where by inference the cardiac output response to exercise was limited by CHF, the VE/V_{CO_2} slope was steeper than normal (as in the non-paced patients) and it could then be increased further by switching pacing modes to reduce acutely the cardiac output response to exercise.

Table 5 demonstrates that the greater exercise related ventilation in patients with CHF and fixed compared with rate responsive pacing was associated with no difference in tidal volume, indicating no change in the relative contribution of anatomical dead space to the total dead space ventilation.

Discussion

This study confirms the increased ventilatory cost of CO_2 elimination in patients with CHF (group 1) relative to normal controls (group 2).[7] It confirms that the VE/V_{CO_2} relation is linear throughout exercise,[2 5] and that its slope is inversely related to peak V_{O_2} below a threshold of about 20 ml/min/kg.[7] It shows also that this is independent of the aetiology of heart failure, a syndrome defined here by reference to resting left ventricular function.

Table 4 Effects of rate responsive and fixed rate pacing on exercise responses in pacemaker dependent patients with and without chronic heart failure (CHF)

	Patients with CHF (n = 6)		*Patiets without CHF (n = 7)*	
	Pacing mode Rate responsive	*Fixed rate*	*Pacing mode Rate responsive*	*Fixed rate*
Exercise duration (min)	10·8 (3·7)†	8·9 (3·1)*†	15·1 (3·1)	12·1 (3·3)*
Peak V_{O_2} (ml/min/kg)	16·1 (3·4)†	13·1 (2·3)*†	20·1 (1·5)	16·9 (0·9)*
RERmax (V_{CO_2}/V_{O_2})	1·07 (0·03)	1·08 (0·06)	1·04 (0·02)	1·05 (0·04)
Heart rate increment (per min)	49 (5)	—	53 (9)	—
VE/V_{CO_2}				
m	39 (5)†	51 (7)*†	31 (2)	32 (1)
c (l/min)	3·8 (1·5)	3·2 (1·8)	3·8 (1·6)	4·2 (0·5)
r	0·98 (0·02)	0·98 (0·03)	0·97 (0·02)	0·98 (0·03)

Values are mean (SD). *P < 0·05 *v* rate responsive pacing; †P < 0·05 *v* respective control (Student's *t* test). Abbreviations as given in table 1.

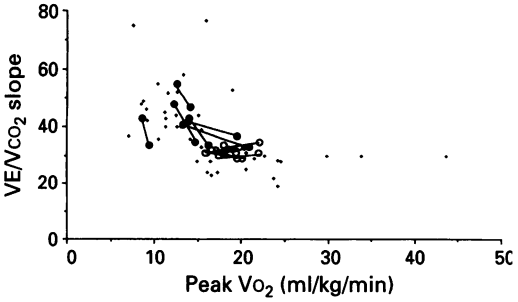

Figure 5 Minute ventilation/minute carbon dioxide production (VE/V_{CO_2}) slope plotted against maximal oxygen consumption (peak V_{O_2}) in pacemaker dependent patients, each pair of joined symbols representing fixed rate and rate responsive pacing mode in that patient. ○, patients with normal resting left ventricular function; ●, patients with impairment of resting left ventricular function; +, patients with CHF (group 1) reproduced from fig 2. Data from pacemaker dependent patients fall within the range represented by patients with heart failure and normal controls. Note that pacing induced reduction in peak V_{O_2} is associated with an increase in the VE/V_{CO_2} slope in patients with CHF but not in those with normal resting left ventricular function.

The data also show that the VD/VT ratio at peak exercise is high in patients with CHF, as previously reported,[2 5] and that it correlates with the VE/V_{CO_2} slope. Arterial P_{aCO_2} and pH remained normal and P_{aO_2} increased during exercise, as previously reported,[2 6 8 9] excluding an abnormality in gas transfer or alveolar hypoventilation. The findings therefore reflect an increase in dead space ventilation (VD). Dead space comprises equipment dead space (constant), anatomical dead space (unaltered if tidal volume is unchanged) or physiological dead space (calculated from the Bohr equation and indicative of relative underperfusion of ventilated alveoli). The increased VE/V_{CO_2} slope thus reflects mismatching between perfusion and ventilation during exercise.

The next part of the study addressed the question of whether or not an abnormally steep VE/V_{CO_2} slope is due to limitation of pulmonary flow with exercise (as is a feature of treated CHF) or whether it is caused by some other feature characterising the syndrome of CHF. This question was addressed by studying patients with coronary heart disease (group 3) in whom exercise tolerance and peak V_{O_2} were limited (at respiratory exchange ratio >1·0) by exercise induced ischaemia and myocardial dysfunction to a level comparable with that in patients with CHF (group 1), but resting left ventricular function was normal. In contrast to those with heart failure, the VE/V_{CO_2} slope in patients with coronary artery disease was normal and, moreover, it showed no relation to peak V_{O_2}.

This suggests that perfusion/ventilation mismatch during exercise depends on the presence of the chronic heart failure syndrome and is not caused exclusively by limitation of cardiac output and pulmonary flow during exercise. As cardiac output was not measured during exercise, this conclusion rests on the indirect evidence that exercise tolerance and peak V_{O_2} were both reduced to the same extent as in CHF, and at a respiratory exchange ratio (V_{CO_2}/V_{O_2}) of >1·0 in each case, indicating anaerobiosis due to limitation of skeletal muscle perfusion. It could be argued that skeletal muscle perfusion does not bear the same relation to cardiac output in patients with CHF as it does in those without it. Evidence of altered skeletal muscle function and peripheral vascular behaviour in chronic heart failure[14–16] would suggest, however, that skeletal muscle perfusion would not become limiting at a *lower* cardiac output in heart failure than in its absence. Cardiac output in patients with coronary artery disease (group 3) would therefore seem not to be overestimated relative to peak V_{O_2}. Moreover, the fact that the VE/V_{CO_2} relation is linear and steeper throughout exercise suggests the presence of an underlying abnormality rather than simply a limitation of cardiac output and pulmonary flow which might appear only towards the limit of exercise tolerance.

The study then questioned whether the VE/V_{CO_2} slope can be altered by interventions which acutely alter the cardiac output response to exercise and thus the overall increase in pulmonary flow. Ethical and logistic considerations precluded direct

Table 5 Minute ventilation (VE), tidal volume (VT), and breathing frequency (Fbr) in pacemaker dependent patients with and without chronic heart failure (CHF) at rest, 6 min exercise (a workload achieved by all patients) and peak exercise

	Patients with CHF (n = 6)		*Patiets without CHF (n = 7)*	
	Pacing mode Rate responsive	*Fixed rate*	*Pacing mode Rate responsive*	*Fixed rate*
VE (l/min)				
Rest	13·2 (1·7)	14·8 (3·4)	11·2 (2·1)	11·9 (1·8)
6 min	28·4 (4·1)	35·3 (5·0)*	23·3 (6·3)	24·4 (6·5)
Peak	51·3 (6·7)	56·1 (7·5)	49·4 (8·0)	44·6 (6·1)
VT (ml)				
Rest	680 (100)	710 (94)	603 (98)	621 (74)
6 min	870 (130)	840 (120)	830 (170)	850 (156)
Peak	1200 (190)	1190 (190)	1250 (190)	1270 (200)
Fbr (breath/min)				
Rest	20 (2)	20 (4)	17 (3)	18 (3)
6 min	32 (5)	42 (6)*	26 (5)	27 (8)
Peak	42 (6)	47 (5)	38 (8)	36 (6)

Values are mean (SD). *P < 0·05 *v* rate responsive pacing (paired *t* test).

measurement of cardiac output. We therefore took advantage of the fact that the exercise related increase in cardiac output is largely dependent on the heart rate response,[17] and that this can be acutely altered in pacemaker dependent patients by switching from rate responsive to fixed rate pacing mode. We confirmed that these patients all demonstrated a lower maximum exercise duration and peak V_{O_2} in fixed rate relative to rate responsive mode. Respiratory exchange ratio at peak exercise was >1 in all cases, indicating limitation of skeletal muscle perfusion and, by implication, of cardiac output (and thus total pulmonary flow) during exercise. In those pacemaker dependent patients who also had CHF with peak V_{O_2} < 20 ml/min/kg, the VE/V_{CO_2} was increased as in other patients with CHF (group 1). Where it was already steeper than normal in these pacemaker dependent patients with CHF, it could be increased further by as much as 30% if the increase in cardiac output with exercise was limited by fixed rate instead of rate responsive pacing. In those pacemaker dependent patients with normal resting left ventricular ejection fraction, however, the VE/V_{CO_2} slope was normal; it remained normal, independent of pacing mode, despite a comparable reduction in exercise cardiac output with fixed rate relative to rate responsive pacing, as reflected in exercise duration and peak V_{O_2}.

Tani and colleagues[18] have reported previously that fixed rate pacing relative to rate responsive pacing reduced exercise tolerance and peak V_{O_2} and increased the VE/V_{CO_2} ratio (measured either at peak exercise or 1 min before the "anaerobic threshold"). In contrast to the present study which shows an increase in the VE/V_{CO_2} slope only in patients with chronic heart failure, the 10 patients in their study had echocardiographically normal left ventricular function. The reasons for this difference are not apparent; five of their patients were studied within 20 days of pacemaker implantation so that abnormalities associated with prior chronic heart failure may have persisted, but the findings seemed to be consistent in all their patients.

The findings of this study, considered together, suggest that the steep VE/V_{CO_2} slope reflects some feature of the chronic compensatory response to the CHF syndrome. Pulmonary microvascular dysfunction is an obvious contender to account, at least in part, for mismatching between perfusion and ventilation mismatch during exercise. The mechanisms underlying the control of microvascular perfusion in any vascular bed are complex. In addition to neurohumoral, metabolic, and chemical influences, and to intrinsic myogenic constriction which may be responsible for autoregulation of flow at different pressure gradients, flow related vasodilatation mediated by endothelium derived relaxant factor (EDRF) is an important integrating influence.[19 20] Experiments with intact systemic vascular beds indicate that flow related EDRF activity coordinates vasomotor behaviour and maintains homogeneity of flow distribution when driven at different flow rates: when EDRF activity was blocked, the microvascular distribution of perfusion no longer remained constant at different flow rates.[21] Abnormalities of systemic microvascular function in chronic heart failure are well recognised.[22–24] Moreover, recent evidence suggests that EDRF activity is impaired in CHF.[25–27] There is, in addition, preliminary evidence that EDRF activity is also impaired in the pulmonary arteries in CHF.[26] The mechanisms underlying these vascular features of chronic heart failure are poorly understood. They do not seem to be associated with fluid retention or haemodynamic factors and are likely to be a consequence of the neurohumoral changes which characterise the syndrome of CHF, and which are activated in response to any condition which prejudices the adequacy of cardiac output.

Dysfunction of pulmonary resistance arteries in chronic heart failure—which may be neurohumorally mediated and which may involve endothelial dysfunction—might thus account for loss of normal homoeodynamic control when overall flow of the pulmonary bed is increased as during exercise. This could interfere with the normal processes of matching perfusion to ventilation. Restoring homogeneity of pulmonary perfusion relative to ventilation might then provide a novel therapeutic approach to the management of exertional dyspnoea in patients with chronic heart failure.

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